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Letter to the Editor

Identifying Swelling-activated Channels from Ion Selectivity Patterns

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The molecular identity of the channels producing swelling-activated Cl conductance (g_{swell}) is of great interest since this physiologic response to swelling is common to many cells. As presented in the May *Perspectives* (Clapham, 1998; Strange, 1998), the question of whether the observed g_{swell} represents a family of channel proteins is presently unanswered, but to be included in this family a channel must be activated by cell swelling and conduct Cl. Determining if a candidate Cl channel should be included based on swelling sensitivity may be problematic since the volume-sensing element could reside in an auxiliary protein that associates with the channel protein and, through allosteric modulation, creates a swelling-activated complex. If the associated sensor is removed inadvertently by experimental manipulation or incomplete reconstitution, then a legitimate family member would be excluded. Permeation selectivity is intrinsic to the pore of the channel protein and thus provides a less easily lost characteristic to aid in identification.

Clearly, permeation by Cl is a characteristic of g_{swell} , but organic osmolytes also flow through these channels at significant rates. Taurine is an important component of intracellular osmolarity in many cell types and can exit through these channels, which indicates a pore large enough for navigation by ions bulkier than Cl. Determination of pore size, to delimit the class of permeating molecules, has been a goal of ion selectivity studies; as pioneered by Hille (1971), the method involves calculating relative permeabilities (P_X/P_{Cl}) from reversal potential measurements combined with knowledge of ion dimensions (using space-filling models) and affinities. A plot of relative permeability versus ion diameter provides insight into pore geometry; P_X/P_{Cl} reported for g_{swell} (Jackson et al., 1994, 1996) are shown in Fig. 1, together with values for CLC-1 (Rychkov et al., 1998), a member of a large Cl channel family. Anion diameter often has been estimated using Stokes' Law for spherical particles (Bormann et al., 1987; Rychkov et

al., 1998); unfortunately, Stokes' diameters often severely underestimate ion size for diameters <1.0 nm (Robinson and Stokes, 1959), which includes most anions and osmolytes of interest during swelling activation. For this reason, molecular sizes obtained from space-filling models are the most appropriate, which suggests that the pore sizes of the GABA and glycine receptor Cl channel family and the CLC family need to be reevaluated.

The permeability patterns for g_{swell} and CLC-1 (Fig. 1) illustrate two distinct classes of anion selectivity. For g_{swell} , the selectivity sequence is lyotropic, $\text{SCN} > \text{I} \approx \text{NO}_3 > \text{Br} > \text{Cl} > \text{F}$, similar to that reported for many anion channels (Frizzell and Halm, 1990) in which larger anions having lower hydration energies pass through the channels more easily than small anions (up to a point set by steric factors). The low field strength sites expected for a pore exhibiting a lyotropic sequence could be formed from the positive ends of the dipoles contributed by the imino groups of the peptide backbone, analogous to the carbonyl oxygen interaction sites of potassium channels (Doyle et al., 1998). Many organic ions also permeate through g_{swell} ; the zwitterionic taurine (2-aminoethanesulfonate) is shown in Fig. 1. Passage of organic ions together with a lyotropic sequence for halide anions is practically identical to the permeation pattern of ions in the so called outward-rectifying Cl channel (ORCC; Halm and Frizzell, 1992). In comparison, CLC-1 has reduced permeabilities for larger anions, $\text{SCN} > \text{Cl} > \text{Br} > \text{I} \approx \text{NO}_3 > \text{F}$, that would suggest steric restrictions limiting flow of bulkier anions such as methanesulfonate (MeSO_3), except that the large polyatomic anion perchlorate (ClO_4) has permeability greater than Cl. Hydrogen bonding of ClO_4 and sulfonates (including taurine) with imino groups could reduce the effective ionic dimensions by up to 0.1 nm, making these ions behave as small as iodide in the pore of such a channel. Low $P_{\text{I}}/P_{\text{Cl}}$ is considered a hallmark of the CLC family, particularly CLC-1, and has been used to suggest that this family of channels does not contribute to g_{swell} .

High P_X/P_{Cl} for ClO_4 and SCN supports a lyotropic sequence (Wright and Diamond, 1977) for CLC-1, similar to g_{swell} . Anomalously low $P_{\text{I}}/P_{\text{Cl}}$ and $P_{\text{Br}}/P_{\text{Cl}}$ re-

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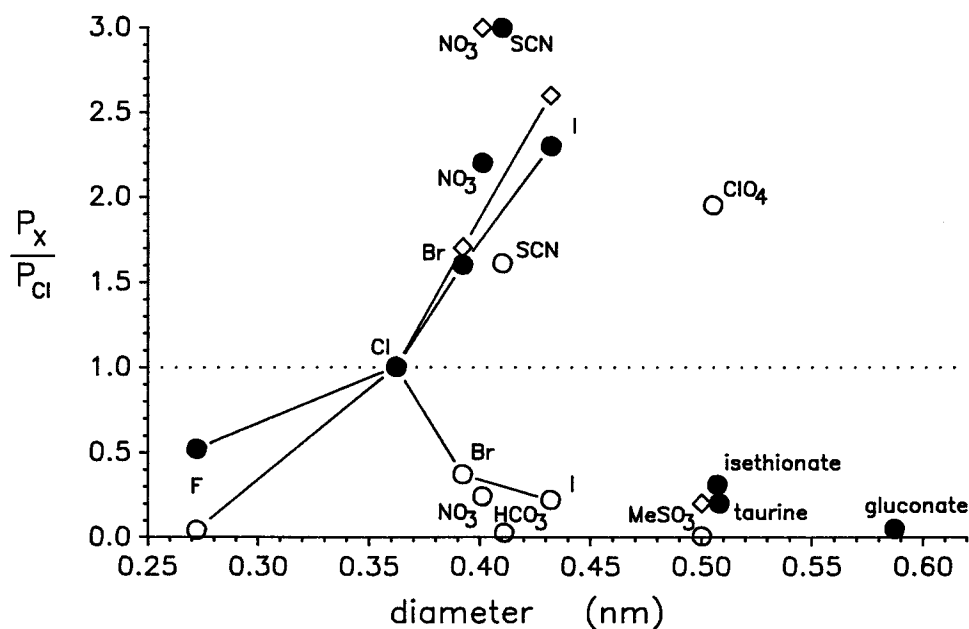


FIGURE 1. Relative permeabilities and diameters of anions. Relative anion permeabilities for g_{swell} (●; Jackson et al., 1994, 1996), CLC-1 (○; Rychkov et al., 1998), and mutant (G230E)hCLC-1 (◇, $P_{\text{SCN}} = 7.2 P_{\text{Cl}}$; Fahlke et al., 1997a) are plotted versus diameters determined from space-filling models (Halm and Frizzell, 1992). Geometric mean diameters were used for the nonspherical ions NO_3 , SCN , HCO_3 , and ClO_4 . Cylindrical diameters were used for the elongated ions methanesulfonate (MeSO_3), isethionate, taurine, and gluconate.

ported for CLC-1 probably result from the current block reported for these ions (Fahlke et al., 1997b; Rychkov et al., 1998); blocking action by permeant ions reduces current, making reversal potential determinations difficult and the resulting P_X/P_{Cl} unreliable. Erroneously low $P_{\text{I}}/P_{\text{Cl}}$ has been recognized in the cystic fibrosis transmembrane conductance regulator Cl channel to result from current block by iodide (Tabcharani et al., 1997). A report on hCLC-1 (Fahlke et al., 1997a) suggests that the taurine mimic MeSO_3 may have a small, nonzero permeability in this channel. Even more dramatic, the anion selectivity of hCLC-1 can be converted by a single amino acid substitution (G230E, a mutation found in myotonia congenita) to a lyotropic sequence, $\text{SCN} > \text{NO}_3 \approx \text{I} > \text{Br} > \text{Cl} > \text{MeSO}_3$ (Fig. 1), suggesting that this mutation relieves iodide block (Fahlke et al., 1997a) such that the resulting larger currents allow a more reliable measure of permeability. In addition, pore dimensions should permit flow of organic osmolytes such as taurine. Interestingly, the glycine at position 230 in CLC-1 is conserved throughout the CLC family, yet wild-type CLC-3 has a lyotropic sequence for halide permeabilities (Fahlke et al., 1997c). Knowledge of permeability for taurine and its mimics in CLC-3 would greatly aid an assessment of the physiologic functions for this member of the CLC family.

Based on what ion selectivity can illuminate about pore dimensions and ion interactions with the pore, the outward-rectifying Cl channel, and members of the CLC family are likely candidates for inclusion in a family of channels producing g_{swell} . Useful probes of permeation by osmolytes such as taurine are ethanesulfonate, isethionate (2-hydroxyethanesulfonate), and ClO_4 ; currents

can be measured directly with these probes since each is a monovalent anion at physiologic pH, and all have similar size and electronic configuration for the anionic part of the molecule. At this time, CLC-3 appears the most likely member of the g_{swell} family, but the allosteric modifications that would occur during physiologic activation (possibly cell swelling) seemingly also could reduce iodide block in other members of the CLC family such that ion permeation measures would be consistent with that of g_{swell} .

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